EXHIBIT 9

American Thoracic Society Documents

Diagnosis and Initial Management of Nonmalignant Diseases Related to Asbestos

CONTENTS

Asbestos is a general term for a heterogeneous group of hydrated magnesium silicate minerals that have in common a tendency to separate into fibers (1). These fibers, inhaled and displaced by various means to lung tissue, can cause a spectrum of diseases including cancer and disorders related to inflammation and fibrosis. Asbestos has been the largest single cause of occupational cancer in the United States and a significant cause of disease and disability from nonmalignant disease. To this demonstrable burden of asbestos-related disease is added the burden of public concern and fear regarding risk after minimal exposure.

This statement presents guidance for the diagnosis of nonmalignant asbestos-related disease. Nonmalignant asbestos-related disease refers to the following conditions: asbestosis, pleural thickening or asbestos-related pleural fibrosis (plaques or diffuse fibrosis), "benign" (nonmalignant) pleural effusion, and airflow obstruction. This document is intended to assist the clinician in making a diagnosis that will be the basis for individual management of the patient. It therefore provides overarching criteria for the diagnosis. specific guidelines for satisfying these criteria. and descriptions of the clinical implications of the diagnosis. including the basic management plan that should be triggered by the diagnosis. It is understood that disease may be present

at a subclinical level and may not be sufficiently advanced to be apparent on histology, imaging, or functional studies.

One of the most important implications of the diagnosis of nonmalignant asbestos-related disease is that there is a close correlation between the presence of nonmalignant disease and the risk of malignancy, which may arise from exposure levels required to produce nonmalignant disease or mechanisms shared with premalignant processes that lead to cancer. The major malignancies associated with asbestos are cancer of the lung (with a complex relationship to cigarette smoking) and mesothelioma (pleural or peritoneal), with excess risk also reported for other sites. There is a strong statistical association between asbestos-related disease and malignancy, but the majority of patients with nonmalignant asbestos-related disease do not develop cancer. On the other hand, the risk of cancer may be elevated in a person exposed to asbestos without obvious signs of nonmalignant asbestos-related disease. However, a diagnosis of nonmalignant asbestos-related disease does imply a lifelong elevated risk for asbestos-related cancer.

DIAGNOSTIC CRITERIA AND GUIDELINES FOR DOCUMENTING THEM

People with past exposure to asbestos consult physicians for many relevant reasons: to be screened for asbestos-related disease, for evaluation of specific symptoms that may relate to past asbestos exposure (known or unsuspected), for treatment and advice, and for evaluation of impairment. In 1986, the American Thoracic Society convened a group of experts to review the literature and to present an authoritative consensus view of the current state of knowledge with respect to diagnosis of nonmalignant disease related to asbestos (2). In 2001, a new group was convened to review and to update the 1986 criteria. This statement constitutes that committee's report, completed in 2004.

The criteria formulated in this statement are intended for the diagnosis of nonmalignant asbestos-related disease in an individual in a clinical setting for the purpose of managing that person's current condition and future health. These general criteria are slightly modified from those presented in 1986 (Table 1) (2):

- Evidence of structural pathology consistent with asbestos-related disease as documented by imaging or histology
- Evidence of causation by asbestos as documented by the occupational and environmental history, markers of exposure (usually pleural plaques), recovery of asbestos bodies, or other means
- Exclusion of alternative plausible causes for the findings

The rest of this statement is largely devoted to presenting clinical guidelines required to document that each of these criteria is met. Demonstration of functional impairment is not required for the diagnosis of a nonmalignant asbestos-related disease, but where present should be documented as part of the complete evaluation. Evaluation of impairment has been exten-

graphic findings (33). These findings established that sheet metal workers, although not working directly with asbestos, had substantial exposure in the work environment.

Measures taken to protect workers, or lapses in these measures, may be important in documenting exposure. Although exposure levels are generally low in developed countries today, lapses occur and were more frequent in the past. Some patients who have immigrated may have worked in countries where occupational health regulations have been poorly enforced or where environmental exposure has occurred.

Environmental sources of exposure, for example, tailings of asbestos mines or prolonged exposure in buildings with exposed sources of asbestos contamination, may be important in some cases. Passive exposure, for example, of children in the home when asbestos is brought into the house on the clothes of a worker, may cause disease (34). Undisturbed and nonfriable asbestos insulation in buildings, including schools, does not present a hazard.

The prevalence of asbestosis among asbestos workers increases with the length of employment, as illustrated in an early report in which investigators analyzed chest films of 1,117 New York and New Jersey asbestos insulation workers. They found asbestosis in 10% of workers who had been employed for 10 to 19 years, 73% among those employed for 20 to 29 years, and in 92% of those employed for 40 or more years (35). A similar exposure–response relationship was found among asbestos cement workers (36).

Differences in solubility among the various types of asbestos may affect fiber retention, body burden, and the risk of nonmalignant disease. The clinician is rarely in a position to evaluate this aspect of exposure and there is no validated means to adjust the occupational history to take this factor into account. Solubility is primarily of concern with respect to projecting future risk, particularly of malignant disease, given a history of exposure. It is irrelevant to diagnosis when disease is already present and other indicators of exposure are demonstrable.

Physical Examination

Physical findings in asbestosis include basilar rales, often characterized by end-inspiratory crackles (rales) (36, 37); in some cases of advanced asbestosis, finger clubbing may be present. Physical findings of crackles, clubbing, or cyanosis are associated with increased risk for asbestos-related mortality (36). Although these physical signs are useful when present, their overall clinical utility is limited by low sensitivity. For example, in one study as many as 80% of individuals with radiographic asbestosis demonstrated crackles, a frequency that appears to be unusually high in the experience of other clinicians (27).

Conventional Imaging

The chest radiograph remains an extremely useful tool for the radiographic diagnosis of asbestosis and asbestos-related pleural disease, and is widely available internationally. The plain film has long been the basis for assessing asbestos-related disease of the lung and pleura. A standardized system for taking and classifying films for presence and profusion of opacities consistent with pneumoconiosis and for pleural changes was developed in the 1950s and is now known as the *International Classification of Radiographs of Pneumoconiosis* (or "ILO classification" after its sponsor, the International Labour Organization). The ILO classification has been revised (38). This system, which is the basis of the "B-reader" qualification for designating persons as competent in classifying pneumoconiosis films, was developed for grading the radiographic severity of pneumoconiosis in epidemiologic studies but has been applied to clinical settings to maintain consistency in classifying chest films. The ILO classification

requires conventional film-based posteroanterior (PA) chest films taken at prescribed specifications and classified with due regard for quality. Conventions for classifying digitized films and other advanced imaging systems have lagged behind the development of technology.

The initial radiographic presentation of asbestosis is typically that of bilateral small primarily irregular parenchymal opacities in the lower lobes bilaterally. Over time, the distribution and density or "profusion" of opacities may spread through the middle and upper lung zones. Although irregular opacities are most common from asbestos exposure, mixed irregular and rounded opacities are often present. The ILO classification profusion score correlates strongly with mortality risk (36), reduced diffusing capacity, and diminished ventilatory capacity (37, 39). A critical distinction is made between films that are suggestive but not presumptively diagnostic (0/1) and those that are presumptively diagnostic but not unequivocal (1/0). This dividing point is generally taken to separate films that are considered to be "positive" for asbestosis from those that are considered to be "negative." However, profusion itself is continuous (36, 38).

Plain chest radiographs are limited with respect to sensitivity and specificity in cases of mild or early asbestosis. Among individuals with asbestosis confirmed by histopathologic findings, 15–20% had no radiographic evidence of parenchymal fibrosis in one study (40), similar to the proportion of other interstitial lung diseases that present with normal chest films (41).

Pleural plaques are frequently documented on plain chest radiographs, but CT is more sensitive for their detection. Only 50 to 80% of cases of documented pleural thickening demonstrated by autopsy, conventional CT, or high-resolution CT (HRCT) are detected by chest radiograph (42, 43). Plain chest radiographs are also limited by specificity in cases of mild pleural disease, which may be difficult to distinguish from extrapleural fat pads (39, 44). Oblique views can enhance both sensitivity and specificity of plain chest radiographs in clinical settings where HRCT is unavailable, but may also fail to distinguish plaques from fat pads (45). CT and HRCT are discussed in the next section.

Computed Tomography

A chest film clearly showing the characteristic signs of asbestosis in the presence of a compatible history of exposure is adequate for the diagnosis of the disease: further imaging procedures are not required. Conventional CT is superior to chest films in identifying parenchymal lesions, rounded atelectasis, and pleural plaques (46). However, conventional CT has been displaced by HRCT for the evaluation of asbestos-exposed subjects because the latter is more sensitive for detecting parenchymal fibrosis.

In subjects with low profusion categories of asbestosis, CT signs tend to be clustered as follows (47):

- Honeycombing and thickening of septa and interlobular fissures, suggesting interstitial fibrosis
- Diffuse pleural thickening, parenchymal bands, and rounded atelectasis, suggesting diffuse fibrosis involving the visceral pleura
- Pleural plaques

HRCT has an important role when experienced readers disagree about the presence or absence of abnormalities on a high-quality chest film, when chest radiographic findings are equivocal, when diminished pulmonary function is identified in association with otherwise normal plain chest radiographic findings, and when extensive overlying pleural abnormalities do not allow a clear interpretation of parenchymal markings. Because HRCT is more sensitive than other techniques for detecting parenchymal changes, it may reveal abnormalities with uncertain prognostic

AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE   VOL 170

TABLE 2. HISTOLOGIC GRADES OF ASBESTOSIS

:hange

ade of severity	
	No fibrosis associated with bronchioles
	Early fibrosis involving walls of at least one respiratory bronchiole, with or without extension into septa of adjacent alveoli; fibrosis confined to alveolated walls of respiratory bronchioles and ducts and not present in more distant alveoli. Alveolitis and inflammation similar to that caused by cigarette smoking
	More severe fibrosis involving acinus: alveolar ducts and/or two or more layers of adjacent alveoli. Normal lung remains in a zone between adjacent bronchioles
III	Fibrosis advanced and coalescent, involves entire acinus; all lung between at least two adjacent bronchioles is affected. Some alveoli are completely obliterated
4 or IV	Honeycomb remodeling and large (up to 1 cm) dilated spaces grossly visible in parenchyma
Grade of extent	
A or 1	Only occasional bronchioles are involved. Most appear normal
B or 2	"More than occasional" but less than half of bronchioles are involved
	More than half of bronchioles are involved

leveloped in	a committee	ollege	rican Pathologist

Iron stains may facilitate recognition of the asbestos bodies; however, the presence of asbestos bodies alone is not sufficient to establish the diagnosis of asbestosis. Asbestosis is associated with a variable degree (usually mild) of chronic inflammation and increased numbers of alveolar macrophages, including multinucleate giant cells. The grades of asbestosis correlate with counts and frequencies of asbestos fibers and bodies in the lung and estimates of cumulative workplace exposure (12, 66) (Table 2).

Only the more severe grades of asbestosis are detectable by gross examination. In its classic form, there is diffuse, bilateral, pale, firm fibrosis most severe in the peripheral zones of the lower lobes. Honeycomb cysts and areas of confluent fibrosis may be present (Figure 7). Milder forms of asbestosis and asbestos-associated small airway disease may not be apparent to gross inspection or to palpation, hence the importance of adequate sampling for histology. This should include peripheral and central areas of all lung lobes (depending on the specimen) as well as portions of visibly diseased lung. Adequate sampling of lung adjacent to resected tumors is particularly important and frequently overlooked or inadequately sampled by pathologists. It is strongly recommended that, when biopsy is performed, thoracic surgeons specifically request additional sampling of lung parenchyma in resected lung specimens from patients with known or suspected asbestos exposure (64, 65).

Asbestosis is more prevalent and more advanced for a given duration of exposure in cigarette smokers, presumably because of reduced clearance of asbestos fibers in the lung (67). Some studies suggest that smokers without dust exposure may show occasional irregular radiographic opacities on chest film, but if so the profusion is rarely as high as 1/0; smoking alone therefore does not result in a chest film with the characteristics of asbestosis (68). Both smokers and ex-smokers have a higher frequency of asbestos-related irregular opacities on their chest radiographs than do nonsmoking asbestos-exposed workers in all profusion categories (68–70). Smoking does not affect the presentation of asbestos-related pleural fibrosis.

Clinical diagnosis. Asbestosis is asbestos-induced pulmonary parenchymal fibrosis, with or without pleural thickening. To diagnose this disorder, one must establish the presence of pulmonary fibrosis and determine whether an exposure has occurred that is of sufficient duration, latency, and intensity to be causal.

Asbestosis becomes evident only after an appreciable latency period, often two decades under current conditions in the United States. In one study of former workers from an amosite asbestos insulation factory that had high levels of asbestos dust, employment for as little as 1 month resulted in a prevalence of 20% of parenchymal opacities 20 years after exposure ceased (70). The

duration and intensity of exposure probably influence the length of the latency period: relatively short-term, high-intensity exposures may be associated with a shorter latency than prolonged, lower intensity exposures.

Asbestosis is usually associated with dyspnea, bibasilar rales, and changes in pulmonary function: a restrictive pattern, mixed restrictive–obstructive pattern, and/or decreased diffusing capacity. The abnormal PA chest film and its interpretation remain the most important factors in establishing the presence of pulmonary fibrosis (Figure 8). Compensation systems may require that the chest radiographs be classified by the ILO system once it is established that the patient has been exposed to asbestos. A profusion of irregular opacities at the level of 1/0 is used as the boundary between normal and abnormal in the evaluation of the film, although the measure of profusion is continuous and there is no clear demarcation between 0/1 and 1/0 (Figure 9). When radiographic or lung function abnormalities are indeterminate, HRCT scanning is often useful in revealing characteristic parenchymal abnormalities as well as correlative pleural changes that are highly suggestive of asbestos exposure, particularly when they are bilateral. The specificity of the diagnosis of asbestosis increases with the number of consistent findings on chest film, the number of clinical features present (e.g., symptoms, signs, and pulmonary function changes), and the significance and strength of the history of exposure.

Although asbestosis is characteristically most advanced and appears earliest in the lower lung fields, there is a rare but well-characterized syndrome of massive bilateral upper lobe fibrosis, in the absence of tuberculosis or lung cancer (71–73).

The characteristic change in pulmonary function observed in asbestosis is a restrictive impairment, characterized by reduction in lung volumes (especially the FVC and total lung capacity), decreased diffusing capacity, and arterial hypoxemia (74, 75). Large airway function, as reflected by the FEV_1/FVC ratio, is generally well preserved. In one of the earliest studies conducted, about 50% of asbestos workers presented with FVC below 80% predicted. The frequency of abnormal vital capacity increased, and the mean vital capacity decreased by 18% over the subsequent 10 years (33, 75). The frequency and magnitude of the restrictive defect increased with ILO category (i.e., increased profusion of irregular opacities) and the presence of pleural changes.

Notwithstanding the predominantly parenchymal and restrictive pattern of the disease, airway obstruction can also be observed and can be seen alone in nonsmokers who have asbestosis. These patients usually have a restrictive pattern of lung function, but clinically they also feature an obstructive component charac-